Remarks/Arguments:

Applicants thank the Examiner for the initialed form PTO 1449, as previously requested.

Claims 17-19, 21-23, and 27-30, previously presented, claims 20 and 24, presently amended, and claim 32, newly presented, are pending.

Claims 1-16, 25, 26, and 31 are cancelled, without prejudice or disclaimer.

Claim 20 is amended hereby to correct a typographical (spelling) error. Claim 24 is currently amended by deleting optional subject matter ("and optionally evaluating"). New dependent claim 32 contains the subject matter deleted from claim 24.

Claims 17-24 and 27-31 stand rejected under 35 USC 103(a) as allegedly unpatentable based on *J. Urol., 161*, 777-792, 1999 (Höltl) in view of *Anticancer Research 17*, 1997, 3117-3120 (Grossmann). Reconsidered is requested.

In the context of a rejection for obviousness under §103, the "*Examiner* bears [both] the initial burden . . . of presenting a *prima facie* case of unpatentability" and "the ultimate burden of persuasion on the issue." *In re Oetiker*, 24 USPQ 1443, 1444 and 1447 (Fed. Cir. 1992) (*emphasis, added*). "The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art *would lead* that individual to combine the relevant references. . . . Indeed, the teachings of the references can be combined only if there is some suggestion or incentive to do so." *Ex parte Obukowicz*, 27 USPQ 1063, 1065 (BPA&I 1992)(*emphasis, added*).

> In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*,[1] preferably in the form of some teaching, suggestion,

> incentive or inference in the applied prior art, that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention [*citations, omitted*].

Ex parte Levengood, 28 USPQ2d 1300, 1300-01 (BPA&I 1993)(*emphasis in original*).

obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself... There must be "something in the prior art to suggest the desirability, and thus the obviousness, of making the combination" [*citation omitted*].

Interconnect Planning Corp. v. Feil, 227 USPQ 543 (Fed. Cir. 1985).

"One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

> It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

In re Hedges, 228 USPQ 685, 687 (Fed. Cir. 1986). It is the combined teachings of the prior art, taken as a whole, which must be considered in an obviousness analysis. *Ryko Manufacturing Co. v. Nu-Star, Inc.*, 21 USPQ2d 1053 (Fed. Cir. 1991).

> When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself... There must be "something in the prior art to suggest the desirability, and thus the obviousness, of making the combination" [*citation omitted*].

Interconnect Planning Corp. v. Feil, 227 USPQ 543 (Fed. Cir. 1985).

Unpatenability of product claims "cannot be predicated on mere conjecture respecting the characteristics of products that might result in the practice of processes disclosed in references." *W.*

L. Gore & Assoc., Inc. v. Garlock, Inc., 220 USPQ 303, 314 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). It is "incongruous" to find "different processes each inherently produce identical products." 220 USPQ at 313.

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). In an obviousness analysis, a reference can not be combined with another reference in such a way that destroys the invention on which one of the references is based. *Ex parte Hartmann*, 186 USPQ 366 (POBdApp 1974). Moreover, references taken in combination teach away when the combination would produce a "seemingly inoperative device." *In re Sponnoble*, 160 USPQ 237, 244 (CCPA 1969).

Obviousness is not established by "the rather general urge commonly felt by alert research men to investigate each new . . . process that appears in order to see if it can be used to improve any of the processes in which they are currently interested."

> An "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, bu the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain conditions were perused.

In re Lilly & Co., 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). *Ex parte Polak*, 83 USPQ 135, 136-137 (POBdApp 1949). "Obvious to experiment" is not the standard for obviousness under §103 of the statute; "selective hindsight is no more applicable to the design of experiments than it is to the

combination of prior art teachings." *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988). Moreover, where the practitioner cannot foresee the results, obviousness to try "*with a reasonable chance of success*" does not distinguish over obvious to try as an improper basis for a finding of obviousness under §103. *Ex parte Old*, 229 USPQ 196 (BPA & I 1985) (*emphasis added*).

A salient feature of the presently claimed invention is that a crude cell lysate is obtained by "freezing" a suspension of treated whole (non-lysed) cells. After thawing, this crude cell lysate (which contains, *i.a.*, fragments of the tumor cell membrane) is mixed and incubated with immature dendritic cells. From this incubated mixture, the mature dendritic cells—which have taken up cytosolic components **and** membrane components (fragments)—are harvested, i.e., the mature dendritic cells present fragments of the molecules they have taken up on their cell surface. Neither these mature dendritic cells nor their method of production—as presently claimed—is taught or suggested by the cited references.

According to Höltl (page 779, left column, "Preparation of Tumor Cell Lystaes") lysates are obtained by applying hypotonic conditions and, then, the"[l]ysates were cleared by centrifugation." In other words Höltl obtains "cleared" lysates by removing the cell membrane fragments and other insoluble material, in order to obtain only the soluble components of the cytosol, which can be isolated as part of the clear aqueous solution (supernatant)—the "cleared" lysates—obtained by centrifugation.

Therefore, Höltl's method does not involve the steps (limitations) of "incubating" a mixture of immature dendritic cells and a cell lysate that contains cell-membrane fragments and, then, "harvesting" mature dendritic cells from this incubated mixture, as recited in present method claims 20-24, 27-30, and 32. Moreover, Höltl's mature dendritic cells, themselves, fail to teach or suggest the mature dendritic cells of present claims 17-19.

Höltl's mature dendritic cells are obtained from the mixture of "cleared" lysates and immature dendritic cells as described in the reference and, so, they do not have tumor-cell-membrane fragments presented on their surfaces. On the other hand, the mature dendritic cells of the present claims *do* have tumor-cell-membrane fragments presented on their surfaces and, so, must *per se* be found different than those disclosed in Höltl; i.e., since the presently claimed mature dendritic cells (product) are obtained by (process) limitations different from those disclosed in Höltl (as explained above), it would be "incongruous" to find, in Höltl, the mature dendritic cells of the present claims. *Garlock, Inc.*, 220 USPQ at 313 (unpatenability of product claims "cannot be predicated on mere conjecture respecting the characteristics of products that might result in the practice of processes disclosed in references").

Grossmann adds nothing to cure the fatal deficiencies in Höltl—either with respect to the presently claimed mature dendritic cells or the presently claimed method. The skilled person would not have been led to combine the teachings of Höltl and Grossmann, contrary to the arguments contained in the statement of rejection.

Grossmann (as pointed out in the statement of rejection) teaches that incubation of tumor cells with IFN-gamma and tocopherol acetate leads to an increase in the amount of *MHC I* presentation. This increase leads to a more efficient recognition by immunocompetent cells and an increase in recruitment of cytotoxic T-lymphocytes. After incubation, Grossman subjects the cells to shock freezing to obtain a crude cell lysate, i.e., cell membrane fragments and other insoluble material are not removed, according to Grossmann.

Höltl, contrary to Grossmann, removes the tumor-cell-membrane fragments *before freezing*, i.e., in order to obtain "clear" lysates (as explained above). Mixing these "cleared" (membrane-fragment free) lysates with immature dendritic cells is necessary, since the immature dendritic cells need to take up *cytosolic extracts* of the tumor cells (effecting antigens in aqueous solution) in order to produce the mature dendritic cells (product) of Höltl.

Accordingly, taking the teachings of Höltl and Grossmann as a whole, as required under §103(a), *Ryko Manufacturing Co., supra*, shows that Höltl indispensably requires use of a "clear"—membrane-fragment free—lysate; whereas, Grossmann indispensably requires use of a crude—membrane-fragment containing—lysate. These inconsistent teachings of the cited references must be considered in the obviousness analysis. *Ryko Manufacturing Co., supra*.

> It is impermissible within the framework of §103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

Hedges, 228 USPQ at 687.

Taking the teachings of Höltl and Grossmann as a whole, including the inconsistent teachings set forth above, which is required under §103(a), *Ryko Manufacturing Co., supra.* demonstrates that the PTO has failed to satisfy its initial burden (establishing a *prima facie* case of obviousness) by presenting "*evidence* . . . that one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention. *Levengood*, 28 USPQ2d at 1300-01(*emphasis in original*). There must be "something in the prior art to suggest the desirability, and thus the obviousness, of making the combination." *Interconnect Planning Corp.*, 227 USPQ at 543. Failing to provide the requisite "suggestion or incentive" to combine Höltl and Grossman, *Obukowicz*, 27 USPQ 1063, the PTO cannot maintain the rejection under §103(a) and, so, withdrawal of the rejection appears to be in order.

Moreover, Höltl teaches away from the presently claimed invention. Höltl "may be said to teach away" from using the crude, membrane-fragment-containing cell lysate as required in accordance with the present claims, because "a person of ordinary skill in the art, upon reading the reference, would be led in a direction, divergent from the path that was taken by applicant." *Gurley*, 31USPQ2d at 1131. Since Höltl teaches away from the presently claimed invention, the rejection under §103(a) cannot be maintained against the present claims. Withdrawal of the rejection appears, further, to be in order.

Additionally, modifying Höltl to use a crude lysate, as taught in Grossman, would have destroyed the invention on which Höltl is based (as explained above). Thus, the references cannot

be combined as alleged in the statement of rejection. *Hartmann, supra.* Withdrawal of the rejection appears, still further, to be in order.

Additionally, applicants submit that Höltl requires time-consuming culturing of the tumor cells, which is not necessary in accordance with the presently claimed invention. Besides, the lysate of Höltl is obtained from cells that were seeded, grown, and harvested, beforehand. In the method of Höltl, it is also necessary to treat the minced tissue with collagenase and deoxyribonuclease before culturing of the cells.

Applicants submit that, at best, in view of Grossmann and Höltl the skilled person might isolate specific antigens from tumor cells incubated with interferon-gamma and tocopherol acetate and use the (isolated) antigens in experiments with dendritic cells, i.e., to test dendritic cells exposed to the antigens as a tumor vaccine. "Obvious to experiment," however, is not the standard for obviousness under §103 of the statute; "selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings." *Dow Chemical Co.*, 5 USPQ2d at 1532.

Indeed, applicants submit that a surprising and unexpected finding underlying the presently claimed invention is that crude tumor lystaes of whole cells, including large membrane fragments, are useful in order to obtain a medicament. That is, the mature dendrite cells, harvested from the incubated mixture of immature dendrite cells and the crude lysate, as presently claimed is surprisingly useful as a medicament, rendering the present claims patentable over the cited references. *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990).

Besides, the teaching of Höltl is even further distinct from the method of the presently claimed invention, because Höltl adds a specific antigen (KLH) to the dendritic cells, when the cells are contacted with the tumor cell soluble lysate. KLH is the immunogenic protein keyhole-limpet hemocyanin, which functions as a helper antigen with adjuvant properties (Höltl page 781, right column, lines 7-9). The helper antigen concept is outlined in Figure 6 of the reference and specifically described in the materials and method section under "Preparation of tumor cell lysates" (Höltl, page 779), and the importance of the helper antigen is stressed (Höltl, discussion on page 781, right column). There is no indication in the publication of Höltl that the method might function without the helper antigen KLH.

In contrast, the antigen preparation of the presently claimed invention is a tumor cell lysate derived from whole cells including membrane fragments, without the need to add an antigen like KLH.

3rd Request for Acknowledgment of Foreign Priority Under 35 USC 119

Applicants request, for the third time, that the Examiner mark the next Office Action to acknowledge receipt of the copy of the certified priority document ("the priority document").

Only the foreign priority claim, by itself, was acknowledged in the instant Office Action. Receipt of the certified copy of the priority document was not acknowledged because, allegedly, the "copy of the certified priority document is not in the application" (Office Action page 2). Refusal to acknowledge receipt of the priority document is improper.

As set forth in the original and repeated requests, the certified copy of the priority document was effectively received by the PTO i.e., in view of Form PCT/IB304, mailed 2 October 2001by the International Bureau, of record (copy attached), establishing satisfaction of PCT Rule 17.1. Accordingly, as required by MPEP 1893.03(c) (emphasis added):

> THE CERTIFIED COPY
>
> The requirement in PCT Rule 17 for a certified copy of the foreign priority application is normally fulfilled by applicant providing a certified copy to the receiving Office or to the International Bureau within 16 months from the priority date. The stamped copy of the priority document sent to the U.S. Patent and Trademark Office from the International Bureau is acceptable to establish that applicant has filed a certified copy of the priority document. The examiner should acknowledge in the next Office Action that the certified copy of the foreign priority document has been filed.

Whether the priority document is, now, missing from the PTO application file is irrelevant: since the PTO received the priority document, the PTO must acknowledge its receipt. MPEP 1893.03(c).

In the event that the PTO wants the missing priority document replaced, it cannot ask—let alone require—applicants to do so. Pursuant to PCT Rule 17.2(a) (emphasis added):

> Where the applicant has complied with Rule 17.1(a) or (b), the International Bureau shall, at the specific request of the designated Office, promptly but not prior to the international publication of the international application, furnish a copy of the priority document to that Office. No such Office shall ask the applicant himself to furnish it with a copy.

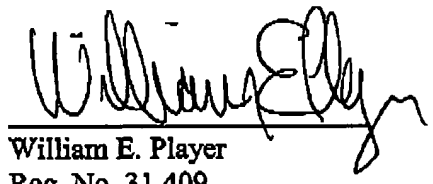
As explained above, the Form PCT/IB/304 of record shows "applicant has complied with Rule 17.1(a)" and, so, the PTO cannot "ask the applicant himself to furnish it with a copy." If the certified copy is missing from the PTO file, the PTO must look to the International Bureau for a replacement. *See* MPEP 1896(III).

Attorney Docket No. P67344US0
Application No. 09/926,630

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 

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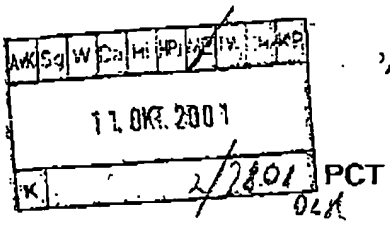

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

MEYERS, Hans-Wilhelm
Postfach 10 22 41
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ALLEMAGNE

COPY

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 02 October 2001 (02.10.01)	
Applicant's or agent's file reference 011300woMetg	**IMPORTANT NOTIFICATION**
International application No. PCT/EP01/08455	International filing date (day/month/year) 21 July 2001 (21.07.01)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 28 July 2000 (28.07.00)
Applicant LIPONOVA GMBH et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
28 July 2000 (28.07.00)	00116362.5 ✓	EP	10 Sept 2001 (10.09.01)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Leslie BARRIOS les
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Form PCT/IB/304 (July 1998) 004397445